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14. ABSTRACT

Lymphedema is a common, chronic, and potentially devastating complication of primary breast cancer therapy. Radiation increases patients' lymphedema risk up to 36% as conventional fields irradiate vital lymphatic tissues. Fusion imaging technologies that combine anatomical and physiological data, e.g. SPECT/CT, may identify lymphatics critical for arm drainage and allow the creation of conformal radiation treatment fields that minimize the exposure of lymph nodes (LNs) and vessels while delivering therapeutic doses to target tissues. This study uses SPECT/CT scanning to localize lymphatics critical for arm drainage, and has established the feasibility of fusing SPECT/CT images with the CT scans used for radiation planning, thereby creating the opportunity to spare essential LNs needless radiation. The research for this project was conducted in two phases. The first involved estimating the levels of incidental, non-therapeutic radiation delivered to the lymph nodes essential for arm drainage following axillary surgery for breast cancer. The second involved estimating the dose reduction in levels of incidental radiation to critical "arm-draining" lymph nodes that could be achieved by integrating SPECT/CT images into the radiation planning process. In the second study, among 28 patients the mean lymph node radiation exposure was 23.6 Gy (SD 18.2) with the standard and 7.7 Gy (SD 11.3) with the SPECT/CT modiifed plans ($p < 0.001$). These studies realized the BCRP goals by elucidating a novel means of refining breast cancer treatment to minimize patients' risk of developing the most prevalent and dreaded complication of conventional therapy, lymphedema.

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Introduction:

The aims of this career development award were expanded to include a pilot study made possible through discoveries made while conducting aim 2 and are now three-fold. The award's two initial aims; 1) training of the recipient, Dr. Cheville, in the conduct of responsible research and 2) conducting a prospective cohort study to estimate the association between radiation dose delivered to the axillary lymph nodes (LNs) and development of lymphedema (LE), were completed in 2008. The 3rd aim of piloting a novel approach to SPECT/CT-based radiation planning developed during execution of the 2nd aim, has now been completed and is detailed in this report.

LE is considered the number one survivorship issue by breast cancer patients.[1] LE has recently been identified as a cause of significantly elevated medical expenditures.[2] Its degrading impact on the quality of life of affected breast cancer survivors has been extensively described.[3-6] Breast cancer treatment modifications that minimize damage to the lymphatic system remain the most effective strategy for reducing LE among breast cancer survivors.[7] Thus far such treatment modifications have been restricted to surgical approaches even though radiation damages lymphatics and significantly increases patients' LE risk.[8]

In order to complete the award's 2nd aim, Dr. Cheville's research team manually fused SPECT/CTs and radiation planning CT scans in order to precisely quantify the radiation dose delivered to the axillary lymph nodes essential for arm drainage. This approach allowed more precise estimation of the contribution of radiation to LE causation than has been possible in the past. Dr. Cheville and colleagues noted that over 40% of patients receive potentially damaging doses of <u>incidental</u> radiation to the lymph nodes critical for arm drainage. Incidental radiation refers to exposure that is not intentional for planned therapeutic benefit. Thus incidental radiation confers no patient benefit, only harm. The fact that almost ½ of patients whose lymph nodes do not harbor cancer cells are none-the-less receiving potentially harmful does of radiation to their axillary lymph nodes suggests that minimizing incidental exposure may reduce LE incidence and severity.

It became apparent over the course of completing the 2^{nd} award aim, that the approach initially conceived for purely investigational purposes, might be clinically applied to minimize incidental radiation exposure to axillary lymph nodes essential for arm drainage, thereby reducing patients' risk of developing LE. The feasibility of this prospect was enhanced by the technological progress that has occurred since the award was initially granted. The latest generation of SPECT/CT scanners and improved radiation treatment planning software collectively offer the capacity to realize the possibility of lymph node sparing without compromising local cancer control.

In order to explore the possibility of utilizing novel SPECT/CT technology to inform radiation planning so that the axillary lymph nodes critical for arm drainage might be spared, we undertook a prospective cohort study. This prospective cohort study was designed to: 1) establish the feasibility of modifying radiation plans in order to spare *arm*-LNs by fusing SPECT/CT images with radiation simulation CTs, 2) estimate the radiation dose reduction achieved by use of SPECT/CT modified radiation plans, and 3) estimate the incidence of LE following SPECT/CT-informed radiation.

Body:

Aim 1. Complete course work and a thesis for a Masters of Science degree in clinical epidemiology and the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

Status: Completed

Dr. Cheville, was awarded the degree of Master of Clinical Epidemiology on May 15, 2006. Dr. Cheville's thesis was substantially edited and reduced in length to meet the publication requirements of current cancer journals. The resultant article, "Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer" has been published.[9] Additional analyses conducted during Dr. Cheville's biostatistical training for her masters' degree have also been published.[10, 11]

Aim 2. Conduct a prospective cohort study to estimate the association between radiation dose delivered to the axillary lymph nodes (LNs) and development of lymphedema (LE)

Statis: Completed

This prospective cohort study was completed in 2008 and the results have been published in two manuscripts.[12, 13] This work established proof of concept for using SPECT/CT to estimate radiation dosimetry to physiologically relevant lymph nodes. Additionally, it was the first to precisely quantify the incidental radiation delivered to the axillary lymph nodes that drain the arm following breast cancer surgery.

Over one third of arm-draining lymph nodes receive damaging incidental radiation
Figures 1 and 2 are histograms which illustrate the radiation dose delivered to visualized LNs with tangent beam and 4 field configurations, respectively. The Y-axis of each figure represents the percentage of total visualized LNs while the X-axis represents radiation dose in Gy. The percentage of LNs receiving > 40Gy is separately listed in each figure since this is a treatment level associated with lymphatic compromise.

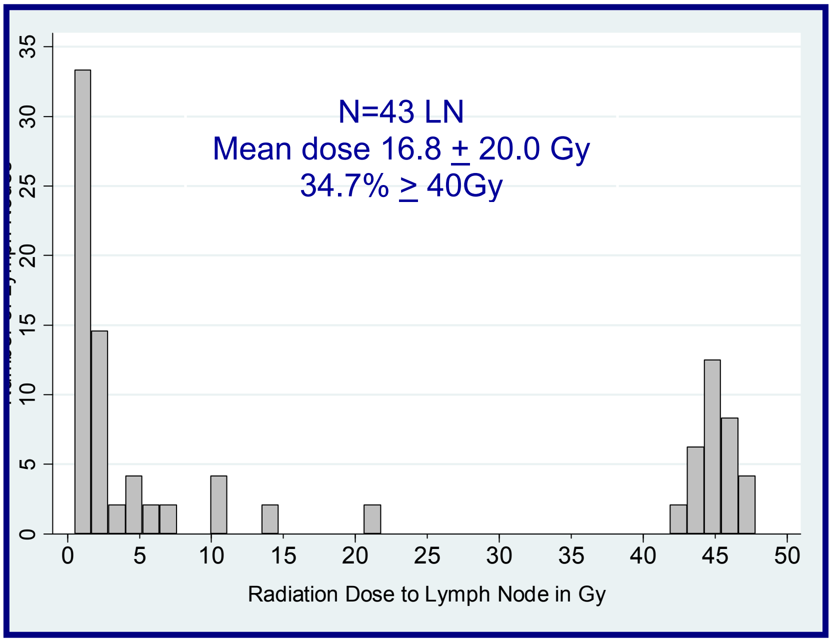

Figure 1. Radiation dose delivered to LNs visualized on SPECT/CT scans and treatment with tangent beam configurations

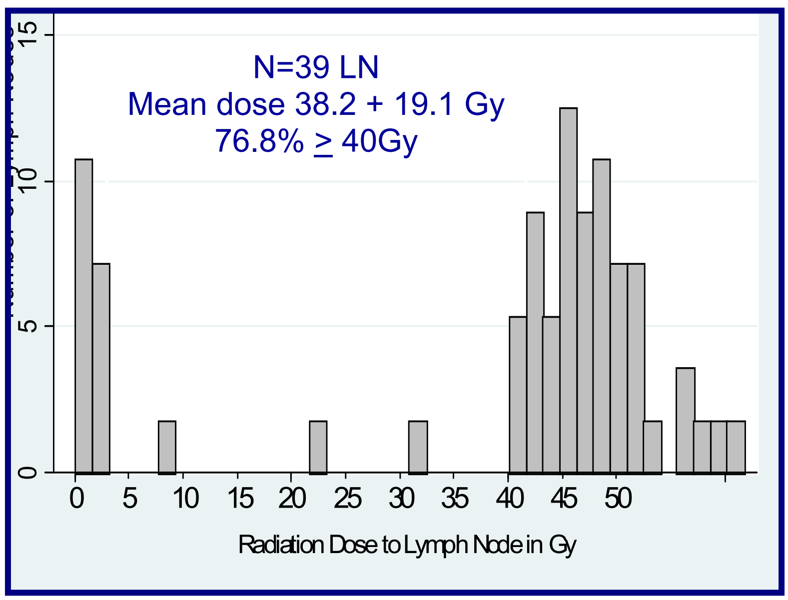

Figure 2. Radiation dose delivered to LNs visualized on SPECT/CT scans and treatment with 4 field configuration (tangent beams + Posterior Axillary Beam + supraclavicular LN irradiation)

The histogram in figure 1 demonstrates that over 1/3 of LNs critical for arm drainage received ≥40 Gy of incidental radiation with tangent beam configurations. The histogram in figure 2 demonstrates that up to 42.9% of visualized LNs treated with 4-field configuration received less that the recommended dose of 45 Gy. 4-field beam configurations deliberately target LNs with the intention of sterilizing any residual tumor cells. These data indicate a high prevalence of subtherapeutic radiation dosimetry to LNs targeted with 4-field beam configurations.

Radiation continues to undermine lymph node function in the years following treatment

Evaluation of follow-up SPECT/CT scans obtained 12-24 months following completion of radiation treatment reveals a strong association between radiation dose delivered to individual lymph nodes and the continued functioning of these lymph nodes in follow up SPECT/CT scans. Lymph nodes that did not receive ≥ 40Gy continue to uptake tracer normally in follow up scans as illustrated in Figure 3. In contrast, a majority of lymph nodes that received ≥ 40Gy could note be identified on follow up scans suggesting that

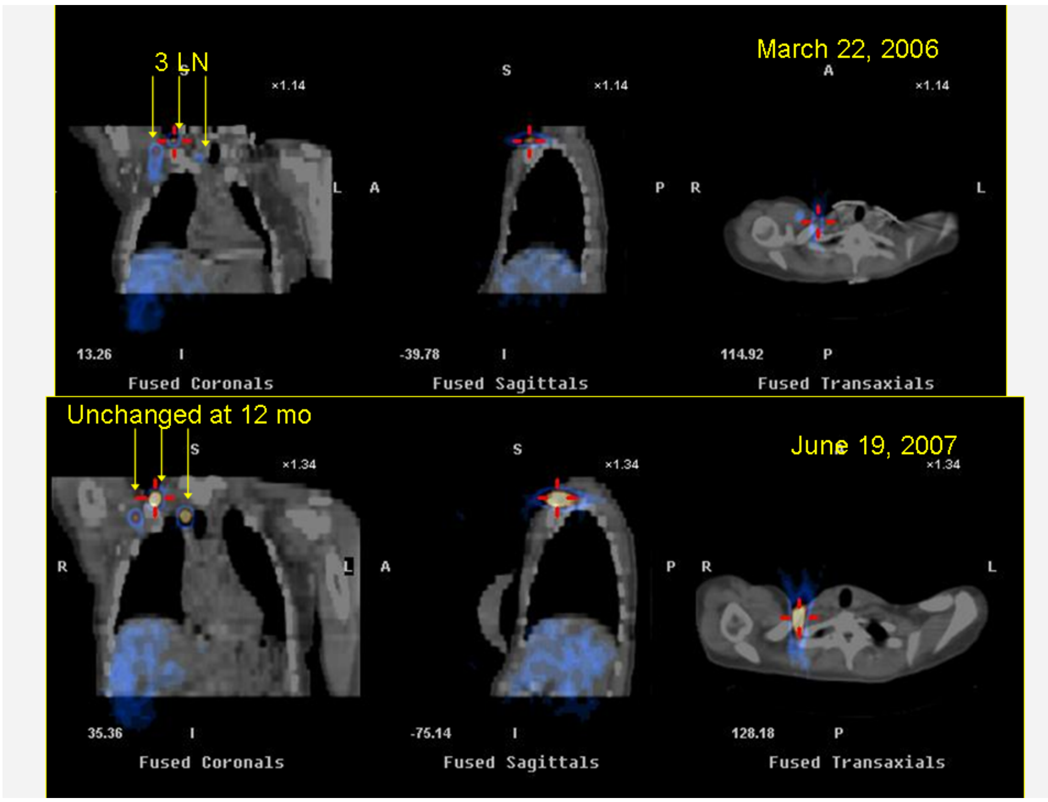

Figure 3. Pre-radiation and follow-up SPECT/CT scan demonstrating sparing of lymph nodes that received < 40Gy.

irradiation renders lymph nodes dysfunctional. Figure 4 illustrates the failure of 7 lymph nodes to appear on follow up scans in a patient whose pre-irradiation SPECT/CT revealed 10 lymph nodes. Similar to other study participants who lymph nodes received > 40Gy, the participant whose scan appears in figure 4 developed LE.

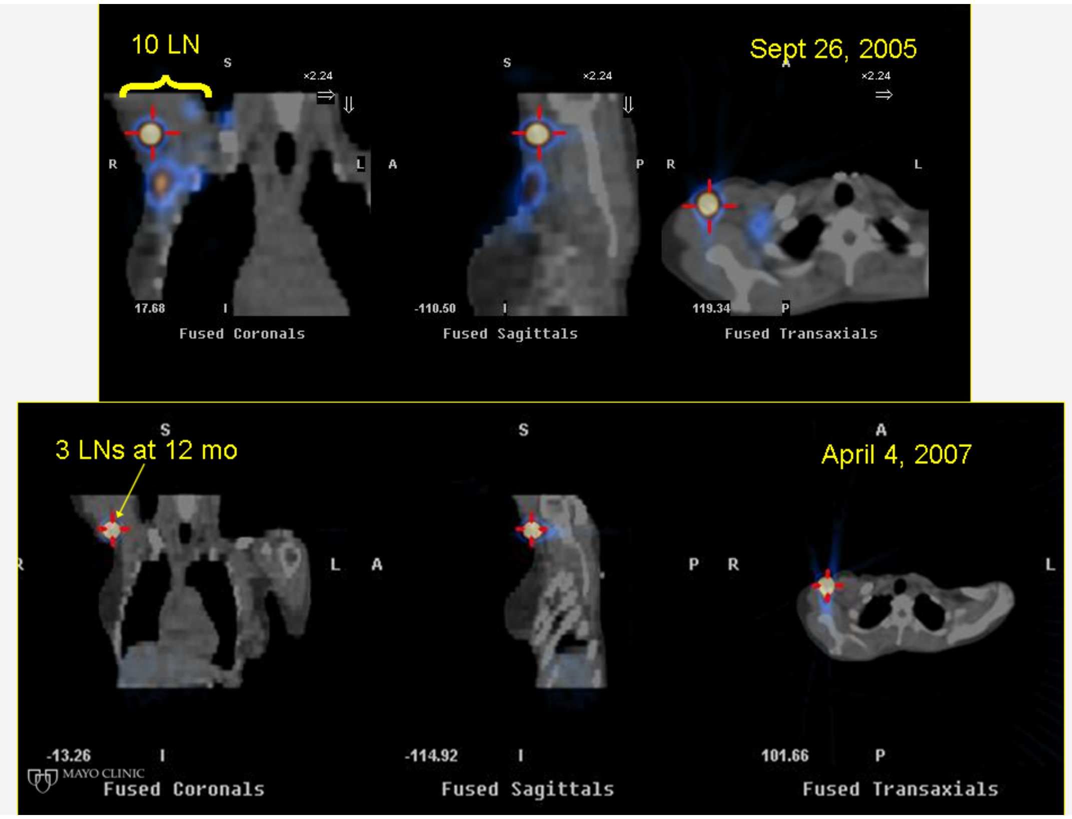

Figure 4. Pre-radiation and follow-up SPECT/CT scan illustrating disappearance of lymph nodes irradiated with > 40 Gy.

Aim 3. Conduct a prospective cohort study to establish the feasibility of modifying radiation plans in order to spare *arm*-lymph nodes by fusing SPECT/CT images with radiation simulation CTs.

Statis: Completed

Among 28 participants, sixty-eight (68) Level I-III *arm*-draining lymph nodes were identified, 57% of which were inside conventional tangent fields but could be blocked by integrating SPECT/CT into the radiation planning process without sacrificing the delivery of therapeutic radiation to target tissues. Sixty-five percent of *arm*-draining LNs in the unmodified vs. 16% in the modified plans received a mean of ≥10Gy, and 26% in the unmodified vs. 4% in the modified plans received a mean of ≥40Gy. Mean LN radiation exposure was 23.6 Gy (SD 18.2) with the unmodified and 7.7 Gy (SD 11.3) with the modified plans ($p < 0.001$). No participant developed lymphedema. These results supported the conclusion that the integration of SPECT/CT scans into breast cancer radiation treatment planning reduces unnecessary *arm*-draining LN radiation exposure and may lessen the risk of lymphedema. A manuscript detailing these results has been accepted for publication by the International Journal of Radiation Biology and Physics. It is currently in press. More precise details from the manuscript are outlined below.

Gamma Camera Image Findings

Excluding a single LN that appeared in one participant's cubital region, the mean time for *arm*-LNs to appear on serial gamma camera images was 42.9 minutes (SD 28.0), with a range of 5 to120 minutes.

SPECT/CT Scan Findings

Arm-LNs were identified in the SPECT-CT images for every participant, with an average of 2.4 (range of 1 to 5) nodes per patient. Among the 69 visualized LNs, 49 (71%), 11 (16%), and 8 (12%) were located in anatomic Levels I, II, and III, respectively.

SPECT/CT-based radiation planning

Overall, the mean radiation (mRT) exposure for all 68 Level I, II and III LNs was 23.6 Gy (SD 18.2) with the unmodified and 7.7 Gy (SD 11.3) with the modified plans ($p < 0.001$) which corresponds to a dosage reduction of 15.9 Gy (67.3%) with the incorporation of SPECT/CT imaging into the radiation planning process. Figure 5 presents details of unmodified standard (STD) vs. modified (MOD) treatment plans for the 68 Level I-III *arm*-LNs. Among the 45 LNs located within STD fields, the mRT was 34.2 Gy (SD 12.5) with the STD plans and 10.6 Gy (SD 12.9) with the MOD plans ($p < 0.001$), a reduction of 23.6 Gy (69.0%).

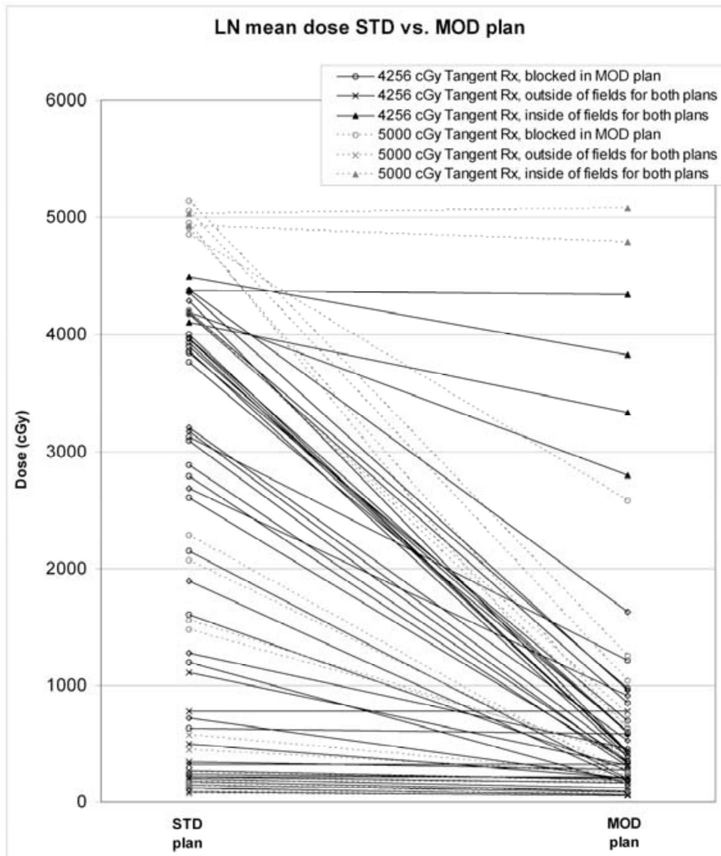

Figure 5

More specifically, among the 28 participants, 3(11%) had all their *arm*-LNs (7 nodes in total) outside the STD treatment fields; 12 (43%) had all of their *arm*-LNs blocked as a result of the MOD protocol (20 nodes in total); and 13 (46%) had at least one *arm*-LN within the STD treatment field and at least one *arm*-LN partially blocked (17 nodes outside STD treatment field, 19 nodes blocked, and 6 nodes received incidental, but therapeutic levels of radiation treatment).

Thirty-nine (57%) of the 68 Level I-III visualized *arm*-LNs were located within the STD treatment fields and were blocked. Among these 39 *arm*-LNs, mRT was ≤10 Gy for 2 of these 39 nodes with the STD and all 39

nodes with the MOD plan. The reduction in mRT dose delivered with the MOD plan relative to the STD plan was greater than 10 Gy for all but 3 LNs (median difference: 28 Gy; Interquartile range[IQ]: 18 Gy-35 Gy).

Twenty-three (34%) of the 68 Level I-III visualized *arm*-LNs, were located outside of the STD treatment fields. Mean radiation (mRT) exposure to each of these LNs was less than or equal to the damage threshold of 10 Gy for 22 of these 23 nodes with the STD, and all 23 nodes with the MOD plan. The reduction in mRT dose delivered to these 23 LNs with the MOD plan relative to the STD plan was less than 4 Gy for all but 1 LN (median difference: 0.5 Gy; Interquartile range[IQ]: 0.1 Gy-0.8 Gy).

Six *arm*-LNs (9%) were located within the STD treatment fields but could not be blocked due to proximity to target tissues and as such the mRT to each of these nodes was >10Gy with both STD and MOD plans.

We calculated the percentage of *arm*-LNs that received threshold radiation doses with the STD and MOD plans in 10 Gy increments: ≥ 50 Gy – STD 4%, MOD 1%; ≥40 Gy – STD 26%, MOD 4%; ≥30 Gy – STD 44%, MOD 7%; ≥20 Gy – STD 54%, MOD 7%; ≥10 Gy STD 65%, MOD 16%.

Onset of lymphedema: No participant developed LE per CTC v.3.0 criteria.

Key Research Accomplishments

1. Precise anatomic localization of LNs draining the arm using dual-head Millennium VG gamma camera (GE Healthcare, Waukesha WI) with Hawkeye single-slice CT to generate fusion SPECT/CT images.

2. Manual fusion of GE Hawkeye SPECT/CT scans with CT simulation scans used for radiation planning.

3. Precise estimation of harmful incidental irradiation with tangent beams and subtherapeutic irradiation with 4-field treatment plans.

4. Established that radiation induced damage progressively undermines lymphatic function and contributes to lymphedema up to 2 year following completion of therapy.

5. Automated fusion of Phillips Precision generated SPECT/CT scans with CT simulation scans using MIMvista software.

6. Established proof of concept that SPECT/CT-informed radiation treatment planning can reduce harmful incidental irradiation to lymph nodes critical for arm drainage.

7. Demonstrated that SPECT/CT-informed planning can safely reduce the incidental, damaging radiation delivered to lymph nodes essential for arm drainage by 67% while effectively treating target tissues.

Reportable Outcomes

1. Manuscripts published describing SPECT/CT-based radiation fusion technique.[12, 13]

2. Platform presentation at the European Society of Therapeutic Radiation Oncology meeting in Barcelona, Spain. August 2007.

3. Platform presentation presented to the National Lymphedema Network meeting in August, 2008.

4. Publication of 4 manuscripts related to work completed during Dr. Cheville's masters' degree training.[9-11, 14]

5. Acceptance of manuscript in top tier radiation oncology journal detailing 67% reduction in harmful, non-therapeutic radiation delivery to arm-draining lymph nodes.[15]

Conclusion

This work to date has established that LNs draining the arm after surgical manipulation of the axilla in the context of primary breast cancer can be localized using SPECT/CT scanning. The radiation dose delivered to LNs can be quantified by both manually and electronically fusing SPECT/CT images with radiation simulation CT scans. Unmodified tangent beams deliver potentially harmful radiation doses to 35% of axillary lymph nodes that are critical for arm drainage, while 4-field irradiation fails to adequately encompass all axillary and supraclavicular lymph nodes. This lack of precision and capacity to individualize treatments may undermine important clinical outcomes including the development of lymphedema and local disease control. Lymphedema develops more frequently in women whose arm-draining lymph nodes receive $\geq$ 40 Gy of irradiation. Automated SPECT/CT fusion with simulation CT scans allows modification of radiation treatment plans to safely reduce the incidental irradiation of axillary lymph nodes critical for arm drainage.

References

1. **Armer JM. The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Invest.* 2005;23(1):76-83.**
2. **Shih YC, Xu Y, Cormier JN, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol.* Apr 20 2009;27(12):2007-2014.**
3. **Maunsell E. *Facteurs de risque de la détresse psychologique chez les patientes atteintes de cancer du sein*. Ottawa: Bibliothèque nationale du Canada; 1989.**
4. **Passik SD, McDonald MV. Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma. *Cancer.* Dec 15 1998;83(12 Suppl American):2817-2820.**
5. **Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Support Care Cancer.* Nov 2005;13(11):904-911.**
6. **Ridner SH. Breast cancer treatment-related lymphedema--A continuing problem. *J Support Oncol.* Sep 2006;4(8):389-390.**
7. **Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst.* May 3 2006;98(9):599-609.**
8. **Meek AG. Breast radiotherapy and Lymphedema. *Cancer.* Dec 15 1998;83(12 Supple American):2788-2797.**
9. **Cheville AL, Troxel AB, Basford JR, Kornblith AB. Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer. *J Clin Oncol.* Jun 1 2008;26(16):2621-2629.**
10. **Cheville AL, Basford JR, Troxel AB, Kornblith AB. Performance of common clinician- and self-report measures in assessing the function of community-dwelling people with metastatic breast cancer. *Arch Phys Med Rehabil.* Dec 2009;90(12):2116-2124.**
11. **Cheville A, Kornblith A, Basford J. An examination of the causes for the underutilization of rehabilitation services among people with advanced cancer. *American J Phys Med Rehabil.* 2011;90(SUPPL.5):S27-37.**
12. **Cheville AL, Das I, Srinivas S, et al. A pilot study to assess the utility of SPECT/CT-based lymph node imaging to localize lymph nodes that drain the arm in patients undergoing treatment for breast cancer. *Breast Cancer Res Treat.* Aug 2009;116(3):531-538.**
13. **Das IJ, Cheville AL, Scheuermann J, Srinivas SM, Alavi A, Solin LJ. Use of lymphoscintigraphy in radiation treatment of primary breast cancer in the context of lymphedema risk reduction. *Radiother Oncol.* Aug;100(2):293-298.**
14. **Cheville AL, Girardi J, Clark M, et al. Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well being. *American Journal of Physical Medicine and Rehabilitation.* In Press.**
15. **Cheville A, Brinkmann D, Ward S, et al. The addition of SPECT/CT Lymphoscintigraphy to breast cancer radiation planning spares lymph nodes critical for arm drainage. *Int J Rad Biol Phys.* In Press.**